REMARKS

With entry of this amendment, claims 1-8, 11, 13-19 and 67-68 are pending in the present application, new claim 68 having been added and claims 9-10, 12 and 20-66 having been previously canceled without prejudice or disclaimer.

The Specification is amended to delete pages "i-ii", corresponding to the Table of Contents.

Independent claims 8 and 11 and dependent claims 13, 15, 16 and 19 are amended to change the term "protein" to "antibody." Claims 5, 7, 16 and 67 are amended to further clarify the claim language. Claims 7, 19 and 67 are amended to correct certain minor typographical errors. Claim 11 is also amended as requested by the Examiner. Support for the amendments to the claims is found throughout the Specification, such as for example at the following: page 11, lines 3-26; and page 18, lines 12-18. Support for new claim 68 is found throughout the Specification, such as for example at the following: page 19, line 27 to page 20, line 2; page 11, lines 3-26; and the example at pages 50-52. No new matter is added by these amendments. No amendment is an acquiescence to any rejection.

Section headings are used in this Amendment for organizational purposes.

Interview Summary

Applicants thank Examiner Yu for the interview with the undersigned representative on December 27, 2005. During the interview, the rejections under 35 U.S.C. § 112, first paragraph, 35 U.S.C. § 102 and 35 U.S.C. § 103 in the Office Action mailed September 9, 2005 were discussed. At the conclusion of the interview, Examiner Yu agreed to reconsider these rejections based on the comments set forth in this amendment.

During the interview, Examiner Yu raised two new formal matters, requesting deletion of the Table of Contents from the Specification and an amendment to claim 11. Applicants have complied with those requests in this Amendment.

Prior Office Action

Applicants thank the Examiner for withdrawing the prior objection to the Specification; the rejection under 35 USC § 112, first paragraph, of claims 8 and 13-19; the rejection under 35 USC § 103(a) of claims 1, 2, 5, 7-13, 16, 19 and 67 over Pohl *et al.*; the rejection under 35 USC § 103(a) of claims 1, 3, 8, 11, 14, 16 and 18 over Pohl *et al.* and further in view of Barth *et al.*; and the rejection under 35 USC § 103(a) of claims 1, 4, 6, 8, 11, 15 and 17 over Pohl *et al.* and in view of Barth *et al.* and further in view of de Costa *et al.*

Information Disclosure Statements

Applicants do not appear to have received acknowledged (initialed) copies of the Second Supplemental Information Disclosure Statement (submitted March 18, 2002) and the Third Supplemental Information Disclosure Statement (submitted October 2, 2003). Acknowledged copies of these IDS's do not appear to be posted on the Public PAIR page for this application. Applicants request the Examiner confirm these IDS's have been considered and acknowledged or, if needed, consider and acknowledge these IDS's.

Applicants also submit herewith a Sixth Supplemental Information Disclosure Statement citing fifteen additional references. Copies of thirteen references are included in this submission. The remaining two references are U.S. patent publications available through PAIR. Applicants respectfully request the Examiner consider these references.

Claim Rejections – 35 U.S.C. § 112, First Paragraph

Claims 8, 11 and 13-19 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner acknowledges that the claims are enabling for an antibody that competes for binding to CD30 with AC10 or HeFi-1, but asserts the claims are not enabling for any other type of protein. In particular, the Examiner argues that claims are not enabled for non-anti-CD30 antibodies.

Without acquiescing to the rejection, but to proceed with more compact prosecution, Applicants have amended claims 8 and 11 to recite the protein is an antibody. Corresponding amendments have been made to the claims depending from

claims 8 and 11. Because the Examiner stated the subject matter of amended claims 8 and 11 is enabled, Applicants respectfully request the Examiner reconsider and withdraw the rejection.

Claim Rejection – 35 USC 102

Claims 11 and 13-19 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Falini *et al.* (Blood 85:1-14 (1995)). The Examiner alleges, *inter alia*, that "any murine antibody, even without CD30 binding capacity inherently comprises a protein comprising at least 95% identity to the instant SEQ ID NO:2" (*see* Office Action, page 6).

Applicants respectfully disagree. Initially, Applicants note that SEQ ID NO:2 discloses an amino acid sequence corresponding to a heavy chain variable region, not a light chain variable region. This point was clarified in Applicants' response to the April 3, 2003 Office Action (referred to by the Examiner in the September 9, 2005 Office Action). (*See* Amendment Under 37 C.F.R. § 1.111, dated October 2, 2003, page 7; *see* also Specification, page 9, Table 1.)

Applicants disagree with the Examiner's argument that "any murine antibody, even without CD30 binding capacity[,] inherently comprises a protein comprising at least 95% identity to instant SEQ ID NO:2." The sequence identity recited in Claim 11 is between SEQ ID NO:2 and a corresponding sequence of another antibody (e.g., another antibody heavy chain variable region). This claim language recites at least 95% sequence identity of between these regions of the antibodies.

Further, the amino acid sequence of any given mouse heavy chain variable region is not necessarily at least 95% identical to the amino acid sequence of another mouse heavy chain variable region. Heavy chain variable regions contain three CDR's disposed within framework regions. The sequence identity between antibody heavy chain variable regions will vary, depending on the amino acid sequences of the CDR's as well as variability in the amino acid sequence of the framework regions. For example, referring to pages xv-xvi of Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, Fifth Edition (1991), a heavy chain variable region has about 110 amino acid residues

(although this length can vary to some extent). (A copy of these pages is submitted in the Sixth Supplemental Information Disclosure Statement.) The CDR's are generally located at positions 31-35, 50-65 and 95-102. The CDR's can comprise about 28 (more or less) of about 110 residues or about twenty five percent of a heavy chain variable region. The framework regions then comprise about seventy five percent of a heavy chain variable region. Thus, for a heavy chain variable region to be at least 95% identical to a second heavy chain variable region, some conservation of the amino acid sequences of the variable region CDR's is also required. Therefore, any given murine antibody variable region is not necessarily at least 95% identical to another antibody variable region.

The Examiner further argues that claims 11 and 13-19 do not exclude a protein with a cytotoxic agent attached to it, and therefore asserts these claims are anticipated by the Ber-H2-ricin conjugate disclosed by Falini *et al.* (Blood 85:1-14 (1995)). Applicants agree instant claim 11 and the claims depending therefrom can encompass an antibody-drug conjugate.

However, the amino acid sequence of the heavy chain variable region of Ber-H2 has different CDR amino acid sequences. Applicants refer the Examiner to SEQ ID NOs:1-3 of WO 97/17374 (submitted in the Sixth Supplemental Information Disclosure Statement). The amino acid sequence set forth in SEQ ID NOs:1-3 is believed to be the heavy chain variable region sequence of Ber-H2. A comparison of SEQ ID NO:2 of Applicants' application with SEQ ID NO:2 of WO 97/17374 reveals the sequences have about 70% identity, which is less than the at least 95% recited by claim 11. (A copy of the "Blast 2 Sequences results" is submitted in the Sixth Supplemental Information Disclosure Statement for the Examiner's review. In this comparison, "Query:" is SEQ ID NO:2 from the instant application and "Sbjct:" is SEQ ID NO:2 of WO 97/17374.) Applicants also invite the Examiner to independently compare these sequences.

Applicants therefore request the Examiner to reconsider and withdraw this rejection.

Claim Rejection – 35 USC 103

Claims 1-8 and 67 stand rejected as allegedly obvious over Tian *et al.* (Cancer Res. 15:5335-41 (1995)) in view of Falini *et al.* (Blood 85:1-14 (1995)). The Examiner alleges, *inter alia*, that Tian *et al.* disclose that the M44 and HeFi-1 antibodies showed a significant antitumor effect by in vivo models of ALCL-expressing CD30. The Examiner acknowledges that Tian *et al.* do not teach treatment of Hodgkin's disease cell line cells or in vivo treatment of Hodgkin's disease. The Examiner argues instead that Falini *et al.* teach, *inter alia*, "how to evaluate cytotoxic effect of an antibody on the Hodgkin's disease cell line cells had been well known in the Hodgkin's disease treatment art." The Examiner further alleges that Falini *et al.* teach the similarities between ALCL and Hodgkin's disease and concludes that Falini *et al.* "suggest[] what would work for Hodgkin's disease might also work for ALCL and vice versa" (emphasis added).

To establish a prima facie case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. There must also be a reasonable expectation of success. Finally, the references must teach or suggest all of the claim limitations. (*See* MPEP § 2142.)

Applicants respectfully traverse this rejection, and submit claims 1-8 and 67 (and to the extent applicable, new claim 68) are not obvious in view of the asserted combination of references because a prima facie case has not been established.

There is not a proper motivation to combine Tian *et al.* and Falini *et al.* References relied on in making a rejection under 35 U.S.C. § 103(a) must be considered in their entirety, including disclosures that teach away from the claimed invention. (*See, e.g.*, MPEP § 2141.02.) "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be lead in a direction divergent from the path that was taken by the application." *In re Gurley*, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

Applicants respectfully disagree with the Examiner's interpretation of Falini *et al.* The Examiner argues that Falini *et al.* teach the similarities between ALCL and Hodgkin's Disease, "thus suggesting what would work for Hodgkin's disease might also work for ALCL and vice versa." The Examiner refers in particular to pages 5-7 of Falini

et al. This section of Falini *et al.* generally discusses the characteristics of ALCL, Hodgkin's Disease and certain other conditions, and that such conditions are associated, *inter alia*, with CD30 expression.

Falini *et al.*, however, discourage the use of unconjugated antibodies in the treatment of Hodgkin's Disease. In particular, Falini *et al.* state as follows:

> Despite optimal in vivo targeting of tumor cells, none of our patients with refractory HD showed a tumor regression in response to the native Ber-H2 antibody. This implies that, for therapeutic purposes, anti-CD30 antibodies should be conjugated to cytotoxic agents (either isotopes or toxins). (*See* Falini *et al.*, page 9, left column (emphasis added; footnotes omitted).)

Therefore, Applicants submit there is not a proper motivation to combine Tian *et al.* with Falini *et al.*

Further, another publication had previously reported that anti-CD30 antibodies had different effects on Hodgkin's Disease cells and ALCL cells. For example, the antibodies M44 and M67 had been reported to stimulate proliferation of T-cell-like Hodgkin's disease derived cell line cells (*see* pages 2049 and 2054 of Gruss *et al.*, *Blood* 83:2045-56 (1994); cited as reference AP in the information disclosure statement submitted in June of 2001). Gruss *et al.* further reported that these mAbs had little effect on Hodgkin's cell line cells of B-cell origin. Gruss *et al.* also reported the effects of these antibodies correlated with the effects of CD30L on the same cell lines.

Falini *et al.* noted the reported differential effects of CD30L on different cell types. In particular, Falini *et al.* cited the Gruss *et al.* article (reference 21) and noted that CD30L had different effects on Hodgkin's Disease-derived cell lines with a T-cell-like phenotype (proliferation) and ALCL cell lines (apoptosis). (*See* Falini *et al.*, page 2, right column, to page 4, left column.) As noted above, Gruss *et al.* taught the M44 and M67 antibodies had the same effects on Hodgkin's Disease-derived cell line cells as did CD30L. Falini *et al.* were aware of the Gruss et al. paper, and thus it is not surprising that they concluded "[t]he CD30 molecule appears an ideal target for immunotherapy of HD or ALCL with anti-CD30 antibodies conjugated to plant toxins or isotopes." (Falini

et al., page 10, left column.) Thus, Applicants submit the skilled artisan, upon reading Falini *et al.*, and knowing of the Gruss *et al.* article, would not have been motivated to try unconjugated CD30 antibodies for the treatment of Hodgkin's Disease.

A prima facie case of obviousness also requires a reasonable expectation of success. Applicants respectfully submit the asserted combination of Falini *et al.* and Tian *et al.* does not provide such an expectation. Tian *et al.* merely proposed that antibodies M44 and HeFi-1 "may be promising agents in the treatment of human $CD30^+$ALCL." (*See* Tian *et al.*, page 5340, right column.) Applicants submit such a proposal is merely an invitation to experiment, and not reasonably predictive of the success of such agents in the treatment of ALCL, let alone Hodgkin's Disease. (*See, e.g.*, MPEP § 2143.02; *see also* MPEP § 2145.) Further, as discussed above, Gruss *et al.* had reported that certain antibodies stimulated proliferation of, or had little effect on, certain Hodgkin's Disease cell lines. Therefore, the asserted combination of references fails to provide a reasonable expectation of success.

Finally, Applicants submit the alleged combination of references does not teach all of the limitations of the instant claims. In particular, Tian *et al.* do not teach or suggest that antibodies M44 and HeFi-1 are effective for the treatment of ALCL. Tian *et al.* are equivocal concerning the use of such unconjugated anti-CD30 antibodies for the treatment of ALCL. For example, Tian *et al.* says, "unconjugated anti-CD30 moAbs may be of potential clinical use" (*see* page 5335, Abstract; emphasis added) and "unconjugated M44 and He-Fi-1 may be of potential use in the treatment of $CD30^+$ ALCL" (*see* page 5341, left column). Referring to the portion of the Discussion cited by the Examiner, Tian *et al.* state:

> Recently, Falini *et al.* (6) provided immunological evidence that the restricted *in vitro* reactivity of an unmodified anti-CD30 moAb (Ber-H2) with normal tissue is maintained *in vivo*, and that optimal *in vivo* targeting of HD cells can be achieved by injecting low doses of Ber-H2. Despite optimal *in vivo* targeting of tumor cells, none of their patients with refractory HD showed tumor regression to Ber-H2, and from this finding, they suggested that, for therapeutic goals, anti-CD30 antibodies should be

> conjugated to other cytotoxic agents (either isotopes or toxins; Ref. 22). However, our data suggest that unconjugated anti-CD30 moAbs can be used, if the antibodies are directed at the ligand-binding site (11). Unconjugated antibodies are attractive, because they avoid the toxicity associated with toxins and isotopes. The results also imply that the sCD30L may be effective against $CD30^+$ tumors. It has been reported CD30 stimulation by a soluble recombinant CD30L inhibited the growth of human ALCL cell lines in vitro, at least in part through the induction of apoptosis (9), in agreement with our results (Fig. 5). This suggests that sCD30L, M44 or HeFi-1 may be promising agents in the treatment of human $CD30^+$ ALCL. (Falini *et al.*, page 5340, left and right columns (emphasis added).)

Thus, even in this discussion, Tian *et al.* are equivocal concerning the use of the antibodies M44 and HeFi-1 for the treatment of ALCL. Applicants submit that such discussion is not sufficient to teach or suggest that the use of antibodies M44 and HeFi-1 would be effective to treat ALCL, let alone Hodgkin's disease.

Falini *et al.* do not overcome the deficiencies of Tian *et al.* because Falini *et al.* teach that results with Ber-H2 antibody imply "that, for therapeutic purposes, anti-CD30 antibodies should be conjugated to cytotoxic agents" (*see* Falini *et al.*, page 9, left column (emphasis added)). Tian *et al.* acknowledge such teaching (stating "they [Falini *et al.*] suggested, that for therapeutic purposes, anti-CD30 antibodies should be conjugated to other cytotoxic agents (either isotopes or toxins; Ref. 22)" (Falini *et al.*, page 5340). Therefore, Applicants submit the combination of Tian *et al.* and Falini *et al.* does not teach or suggest all of the limitations of the instant claims.

Applicants therefore request the Examiner to reconsider and withdraw this rejection.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the instant application. Withdrawal of the Examiner's rejections and allowance and action for issuance are respectfully requested.

Applicants request that the Examiner call the undersigned attorney at (425) 527-4138 if any questions or issues remain.

Respectfully submitted,

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